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Editorial Comment

Increased Myocardial Oxygen Demand and Ischemia During Daily Life: Resurrection of an Age-Old Concept*

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Background. Most patients with myocardial ischemia during daily life have evidence of fixed atherosclerotic coronary artery disease and exercise-induced ischemia. Although an increase in myocardial oxygen demand is generally believed to be primarily responsible for anginal episodes in these patients, the precise mechanism of the genesis of transient ischemic episodes during daily life is controversial. It has been suggested that because most such episodes occur with minimal or no physical activity, a primary reduction in coronary blood flow might play a predominant role. This concept was supported by some studies (1,2) that described relatively small increases in heart rate preceding transient ischemic episodes recorded during ambulatory electrocardiographic (ECG) monitoring. In addition, some data (1) showed that heart rate was lower at the onset of transient ischemic episodes than at the onset of ischemia during exercise testing. Several recent studies including the report by Panza et al. (3) in this issue of the Journal clearly refute these earlier postulates by demonstrating that the vast majority of ischemic episodes during daily life are preceded by an increase in myocardial oxygen demand (3–6).

The present study: the role of increased heart rate in transient ischemic episodes in daily life. In their article, Panza and coworkers (3) provide further evidence supporting the role of increased heart rate in the pathophysiologic process involved in the genesis of myocardial ischemia during daily life. In their study, most ischemic episodes (89%) during ambulatory ECG monitoring were preceded by an increase in heart rate of >10 beats/min. Using heart rate as a surrogate for ischemic threshold, these investigators compared the findings during exercise-induced ischemia with the hemodynamic changes preceding and during transient ischemic episodes recorded by ambulatory ECG monitoring. They demonstrated a strong correlation between the heart rate at the onset of ischemia during exercise testing and that at the onset of ST segment depression during ambulatory ECG monitoring. They were able to demonstrate this correlation primarily because, in contrast to previous workers, they utilized the National Institutes of Health Combined Protocol, which uses slow increases in work load that are more akin to those encountered during unrestricted daily activities (3). Utilizing this unique approach, they also demonstrated a strong correlation between the number of times the degree of heart rate increment during ambulatory monitoring reached the exercise ischemic threshold and the number and duration of ischemic episodes observed during daily life. In the vast majority of patients the heart rate at the onset of ST segment depression during ambulatory monitoring was similar to the heart rate at the onset of ischemia during exercise testing. Only in 15% of ischemic episodes was the heart rate at the onset of spontaneous ischemia during daily life ≥10 beats/min below the exercise ischemic threshold. The duration of heart rate increases associated with ischemic episodes was significantly longer than that of increases in heart rate that were not associated with myocardial ischemia.

These results clearly demonstrate that the pathogenetic mechanism involved in spontaneous ischemia during daily life is quite similar to that responsible for the ischemia produced in the exercise laboratory. Because all patients in this study had evidence of fixed coronary artery disease and exercise-induced ischemia, it should not be surprising to observe that most transient ischemic episodes in these patients were preceded by an increase in heart rate. Nevertheless, the findings of this study are of interest and confirm the results of several other recent studies (4–6) that also demonstrated a definitive role of increase in myocardial oxygen demand in the pathogenesis of ischemia during daily life.

Limitations of the present study. The present study (3) provides clinically relevant and useful information; however, it has some limitations. Although 64% of the patients were asymptomatic and 42% had single-vessel disease, an unusually large proportion (89%) of patients had evidence of ischemia during ambulatory monitoring. In contrast, most previous studies (4–6) have found myocardial ischemia during daily life in only 40% to 60% of patients. Thus, the data reported by Panza et al. (3) might not be applicable to all patients with coronary artery disease. In addition, the authors have not provided details on the correlation between various activities and times of day with the heart rate increases and occurrence of ischemic episodes. This is important missing information because the degree of heart rate increases is known to vary significantly depending on the nature of the activity, the emotional state of the patient and the time of day. Also, the heart rate before each ischemic episode was not analyzed on an individual basis

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with calculation of the percent change from the corresponding baselines during various times of day. Finally, although the authors have used heart rate as a surrogate for myocardial oxygen demand, they did not measure other determinants of oxygen demand such as systemic arterial pressure and cardiac contractility.

Comparison with other studies. The findings reported by Panza et al. (3) are consistent with previously reported data (4–6). Most of the latter studies used heart rate as a surrogate for myocardial oxygen demand and demonstrated that 55% to 80% of transient ischemic episodes were preceded by a significant increase in myocardial oxygen demand (4–6). Utilizing supine bicycle exercise testing with a slow progressive increase in work load in 50 patients, Hinderliter et al. (4) also reported a close correlation between the heart rates asociated with exercise-induced ischemia and those at which ischemia developed during Holter monitoring. The results of these studies (3,4) suggest that the primary reason for the previously described poor correlation between the ischemic thresholds during exercise and Holter monitoring might have been the abrupt increases in work load in the exercise protocols used in those studies (4,5). The total duration of heart rate increases also plays a significant role in the genesis of transient ischemic episodes. McLenachan et al. (5) showed that the heart rate increases associated with ischemia during Holter monitoring were of significantly longer duration than those not accompanied by ischemia.

Although almost all studies have used changes in heart rate as a surrogate for myocardial oxygen demand, relatively few (6,7) have evaluated the role of simultaneous changes in heart rate and blood pressure in the pathogenesis of transient ischemia during daily life. However, the results of those studies demonstrated that most transient ischemic episodes are preceded by significant increases in heart rate and systolic blood pressure. In a study of 30 patients with stable coronary artery disease, we (6) observed that 61% of the ischemic episodes were preceded by a significant increase in heart rate and 73% by an average increase of 10 mm Hg in systolic blood pressure within 6 min before the onset of ischemia. We also found that the morning increase in ischemic activity paralleled the increases in heart rate and blood pressure during this period. Others (8) have shown that the increases in blood pressure and heart rate produced by mental stressors similar to those encountered during daily life can trigger ischemic events in patients with coronary artery disease.

Thus, the available data from several recent studies (3–6) including the current report by Panza et al. (3) clearly demonstrate that most transient ischemic episodes during daily life are preceded by an increase in myocardial oxygen demand. In some cases, however, more than one mechanism might play a role in the genesis of ischemic episodes and a small number of such episodes may well occur as a result of a primary reduction in coronary blood flow.

Clinical implications. The present findings and those reported previously are of clinical importance and provide evidence in support of the well demonstrated efficacy of beta-adrenergic blocking agents in suppressing ischemia during daily life. It is also known that beta-blockers are highly effective in reducing the risk of cardiac death in the postinfarction period. Recent data (9) suggest that this beneficial effect of beta-blockers might indeed be secondary to their anti-ischemic properties. Future studies should evaluate the beneficial effects of therapeutic choices based on the pathophysiologic process in reducing the adverse outcome associated with ischemia during daily life.

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